THE EFFECT OF SOCIAL MIXING PATTERNS ON THE SPREAD OF AIDS

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ABSTRACT

Mathematical models of the transmission of the AIDS virus can help us better understand the spread of the AIDS epidemic and prepare for the future. Model explorations can indicate which factors the epidemic is most sensitive to and provide guidance in designing interventions, educational programs and social behavior studies. We explore the sensitivity of a transmission model to different social mixing patterns. This model continuously distributes a homosexual community according to sexual partner change rates and can account for infectivity and conversion times that vary with time since infection. An acceptance function determines which partners are acceptable to an individual and defines the mixing between groups with different partner change rates. We find that if people only select partners with very similar behavior the epidemic grows much slower than if they are not as discriminating. Therefore, understanding social mixing patterns may be one of the most urgent tasks if we are to anticipate the future. We also find that the epidemic is sensitive to variable infectivity and conversion times.

I. INTRODUCTION

Mathematical models for the spread of the Human Immunodeficiency Virus (HIV) that causes AIDS are tools that have the potential to greatly enhance our understanding of the AIDS epidemic. Models provide a framework within which we can study the interactions of social and biological mechanisms that influence the spread of the disease. They allow us to ascertain the relative influence of various factors on the spread of the epidemic, as well as the sensitivity to uncertainties in values.

As a first step in developing a reliable model, we have developed a deterministic model for a homosexual community. This model distributes the population according to the number of sexual partners per year and keeps

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track of time since infection for infecteds and time since diagnosis for AIDS cases. Susceptible persons are infected through contacts with infected persons, and infected persons develop clinical AIDS (such as Kaposi's sarcoma [KS] or opportunistic infections such as pneumocystis pneumonia [PCP]) at a rate that depends on the length of time since HIV infection. AIDS patients subsequently die at a rate that depends on the length of time since AIDS developed. We assume that an infected person remains infected and infectious for life and that a person maintains the same partner change rates the whole time he remains in the population.

Hyman and Stanley (1988) explored a number of questions with simplified versions of a model similar to the one presented here. They used a model which neglected variations in partner change rates to examine the impact of various plausible shapes for the infectivity as the time since infection varies. These calculations pointed out the importance of measuring the variability of the infectiousness during the disease. They also used a model with no variations with time since infection to show that random partner choice is dramatically different from a strong bias of like prefers like. Other models have also shown that selective partner choice is a crucial determinant of HIV spread (Jacquez et. al., in press, Stigum et al, 1988).

Because different mixing patterns can result in radically different epidemics, much more must be known about the interactions between people that lead to AIDS virus spread before it will be possible to accurately predict the AIDS epidemic. The number of sexual partners that people have, the partner-selection process, and the amount and type of contacts between partners must be understood and correlated with sociological information about the partners, such as how many partners your partners have.

In this paper, we further explore the sensitivity of the model to assumptions about partner choice, again using a model which neglects variations in parameters with time since infection. Then we add the distribution of infecteds with time since infection and parameters that vary with time since infection to see what the effects of these variations are.

In our analysis, we focus on the initial growth of the epidemic. If we are to predict where this epidemic is going, we must fully understand its transient dynamics, including the response to changes in the environment of the epidemic. The epidemic will not reach an equilibrium endemic state for a very long time, partly because of the long conversion times from infection to AIDS, during which a person can transmit the virus and partly because medical advances and changes in lifestyle will greatly modify the future of the epidemic. The infectiousness and susceptibility of high-risk individuals

in the heterosexual community may be significantly reduced if programs are initiated to quickly identify and treat other STDs. More people are being tested for antibodies to HIV and counseled on the implications of the test results. Treatments are being developed that will prolong the lives of infected persons and perhaps lower their infectivity. A partially effective vaccine may eventually be developed. Models can be used to investigate the effects of each of these programs on the course of the epidemic only if they can capture the transients of the epidemic.

As models are developed they will provide a logical structure for the diverse data that researchers are collecting. Also, new questions and insights will arise to guide investigators in directing their research to add to the general understanding of this epidemic.

II. EPIDEMIOLOGY OF AIDS

The HIV that causes AIDS is primarily transmitted through sexual contact (man-woman, man-man), sharing of hypodermic needles, and exposure to infected blood either perinatally or through blood transfusions. HIV is not transmitted by nonsexual daily contacts, even though the virus has been isolated from almost every body fluid (Fischl et al., 1987). The infection risk to an individual depends both on the behavior of the individual and on the prevalence of infection in the groups with which the individual has sexual contacts or shares needles. This prevalence varies between regions and age groups, as well as between behavioral risk groups. Multiple sexual partners, sexual partners in a high-risk group or from a highly populated area and sharing needles when using drugs all increase risk.

Surveys of risk behaviors in the homosexual communities demonstrate that the variance in the number of sexual partners per year is large. (see Fig. 4.3 in Section IV.D). In this epidemic, it is significant that the people with many partners tend to become infected first and then become carriers who infect less-active people. This distribution can have a marked effect on the course of the epidemic and on which risk group is currently at highest risk of infection.

Risk from sexual activity depends on the probability of choosing an infected partner as well as on the number and type of contacts with an infected partner. The probability of choosing an infected partner depends not only on how many new partners are chosen but also on the manner in which those partners are chosen.

The risk group from which a person chooses partners for sex or needle-sharing is an important social question about which little is known. No large-scale studies specifically aimed at sexual behavior have been conducted in the United States since the Kinsey Studies more than 35 years ago and the sampling procedure for this study decreases its usefulness. The information available from other countries is also poor. However, a number of other studies, such as fertility studies, have included some questions on sexual behavior or have studied specific groups. In addition, NICHD is designing and will implement a nationwide survey of sexual behavior and needle-sharing behavior specifically aimed at gathering information about the transmission of the AIDS virus. Surveys of sexual behavior are being conducted or planned in many countries around the world. For example, a national, randomized survey of 10,000 people has recently been conducted in Norway (Sundet, et al, 1988).

Most models for the transmission of venereal diseases (Hethcote and Yorke, 1984; Anderson et al., 1986) have assumed that all partners are picked at random from the pool of available partners. This assumption leads to the proportionate-mixing assumption that the per year probability of someone with i partners per year picking an infected partner with j partners per year is $i \cdot j \cdot P_j / P_T$, where P_j is the number of infected people with j partners per year and P_T is the total number of partners picked per year. These models also assume that the probability of infection per partner is the same. However, it is clear that these assumptions are overly simplistic.

It seems reasonable to assume that there is a tendency for people with fewer partners to have more contacts per partner than do people with many partners. In most communities, there is also a bias of like toward like, so that people with few partners tend to choose partners who also have few partners. This observation led Hethcote and Yorke to use a combination of within-group mixing and random mixing in their 2 risk-level gonhorhea model. Adding these biases into the Anderson et al. model leads to substantially different predictions from their random-mixing model with equal risks (Hyman and Stanley, 1988).

In our model, we assume that an average probability of infection can be assigned to each contact. This assumption may not be sufficiently accurate to predict the spread of HIV and additional factors may need to be included in the model (Peterman, et al., 1988). For example, the probability of infection might depend strongly upon the strain of the virus or on the health of the partners.

The infectiousness of a contact probably also depends on the type of contact (man-man, woman-man, man-woman, anal-genital, oral-genital). There is growing evidence that infectiousness may depend as well on other cofactors such as venereal diseases and the use of protective devices (condoms, nonoxynol-9). We need estimates for the prevalence of these cofactors, how frequently protective devices are used, and how much behavior can be influenced by factors such as education, knowledge that a partner or oneself is infected, and fear of infection. As public awareness increases and more people know they are infected, we speculate that the resulting drift toward safer sexual practices will slow the spread of the virus.

The African epidemic demonstrates that the virus can spread quickly through a heterosexual network. Growing evidence suggests that this fast heterosexual spread is partly due to a high prevalence of cofactors, such as genital ulcers caused by chanchroids, which may greatly increase both infectiousness and susceptability. In the developed world, such severe cofactors are virtually nonexistent. However, other cofactors are present, such as gonorrhea, syphilis, and herpes, that may increase transmission rates less dramatically. Without data on infectiousness, with and without cofactors, male-to-female and female-to-male, it is impossible to tell whether or not a self-sustaining heterosexual epidemic will occur in the United States, even though the current heterosexual AIDS cases are primarily due to contacts with homosexuals and IV drug users. A slowly growing heterosexual epidemic could be masked by cases due to contacts with these groups. It is unlikely that models can distinguish between these two possibilities without estimates of transmission probabilities from partner studies (e.g., Fischl et al., 1987; Padian et al., 1987).

The accumulated number of AIDS cases diagnosed in the United States as reported to CDC, A(t), is not growing exponentially but is well approximated by

$$A(t) = 174.6(t - 1981.2)^{3.0} + 340 \pm 2\% \qquad (2.1)$$

for times $t \geq 1982.5$. This polynomial growth is evident in nearly every CDC-defined category including risk behavior, age, region of the country, and ethnic group (Hyman et al., in preparation). The AIDS cases approximated by Eq. (2.1) are based on the pre-June 1987 AIDS definition and do not include dementia and wasting syndrome.

If $C(\tau)$ is the probability that a person infected with HIV at time $t-\tau$ has developed AIDS by time t, and if $I'(t)$ is the number of people infected per year with HIV, then the cumulative AIDS cases reported to CDC satisfies the

relationship

$$A(t) = p \int_0^\infty C(\tau)\, I'(t-\tau)\, d\tau \tag{2.2a}$$

or

$$A'(t) = p \int_0^\infty C'(\tau)\, I'(t-\tau)\, d\tau \tag{2.2b}$$

where p is the fraction of infected individuals eventually reported to CDC as AIDS cases. p is the product of the probability that an infection will result in a pre-1987.5 CDC-defined AIDS case (which excludes dementia and slim disease) times the probability it will be reported to CDC. The probability that an AIDS case will be reported to CDC is the product of the probabilities that it will be diagnosed and, once diagnosed, that it will then be reported. Using estimates of $C'(\tau)$, the probability density function for conversion to AIDS, we can solve Eq. (2.2) for I'(t).

As the width of $C'(\tau)$ approaches zero (that is, a delta-function), then the solution of Eq. (2.2) approaches

$$I(t) = p^{-1} A(t + \tau_A)\,. \tag{2.3}$$

This estimate can be used as a rough approximation for I(t), even for fairly wide distributions $C'(\tau)$ (see Hyman and Stanley, 1988). This approximation can be used to estimate the number of infected individuals in January 1988. For example, if we assume that 80% of the infected individuals develop CDC-defined AIDS and that 80% of these are reported to the CDC, then p = 0.64. If τ_A = 9 years and the number of AIDS cases in 1997 (= 1988 + τ_A) is 85% of the extrapolated cubic approximation (4.2), then the current cumulated number of infected individuals is

$$I(1988) \simeq \left[\frac{0.85}{0.64}\right]\left|174.6(1988.0 + 9 - 1981.2)^3 + 340\right| \simeq 915{,}000\,. \tag{2.4}$$

We remark that if only 40% of the infected individuals develop CDC-defined AIDS (as was thought a few years ago) then, even though the predicted AIDS cases are the same, this approximation estimates that there would be 1,830,000 people infected with HIV in the United States.

The cubic polynomial growth can be explained by a wave of infection progressing from populations with high-risk behavior into populations with

lower-risk behavior. For example, if individuals with risk behavior r (proportional to the number of sexual partners or needles shared) are infected through interactions with people of similar behavior and if the population is distributed as a decreasing function of risk behavior [e.g., $N(r) \approx N_0(1+ar)^{-4}$, where N(r) is the number of individual with risk r], then the highest-risk population is quickly infected, giving rise to an initial transient exponential growth. This growth quickly becomes polynomial as the saturation wave of infection moves into lower-risk (but still high-risk) behavior and finally slows to an exp(1/t) growth rate (See Sec. V). The polynomial growth is analyzed in more detail in Colgate et al. (1988).

III. MODEL DESCRIPTION

A complete model of the spread of the AIDS virus in a sexually active and IV-drug-using community must account for the complicated interactions between people. However, one must begin by understanding the behavior of simple models before going on to explore more complex ones. In risk-based models, such as the one we use here, the population is stratified according to the amount of risk individuals incur. These models do not model the risk (or protection) of longer-term relations as well as the partnership models of Dietz (1987 and 1988) in which individuals are continually forming and breaking partnerships and the infection is passed only when one individual in the partnership is infected and the other is not. However, in the partnership models it is difficult to account for the wide variations in risk behavior that occur. Because we are primarily concerned with modeling HIV spread in high-risk populations, we use the risk-based approach and account for partnership duration by allowing a variable number of contacts in each partnership.

For modeling purposes, we divide the at-risk community into uninfected susceptibles, infecteds without AIDS, and diagnosed AIDS cases. To model variations in risk behavior within this community, we suppose that the population can be distributed according to their numbers of new sexual partners per year. People mature into a fixed risk group and leave it only upon becoming sexually inactive (and ceasing to share needles). Before the introduction of the AIDS virus, there was a balance between a constant maturation and migration rate into each risk group in the community and a constant rate per individual of retirement or death out of it; these processes continue in the presence of AIDS. Susceptibles become infected through sexual contacts or IV needle-sharing with infected partners. Infected

individuals eventually develop AIDS, becoming sexually (or needle-sharing) inactive, and die at an accelerated rate

We further stratify the non-AIDS-infecteds and AIDS cases according to time since infection or AIDS. This allows us to model both a variable infectivity and the distributions of times from infection to AIDS and of times from AIDS to death. Defining

t	:	time,
τ	:	time since becoming infected or developing AIDS
r	:	number of new sexual partners per year,
$S(t,r)$	:	distribution of susceptibles according to the number of partners per year,
$I(t,r,\tau)$	:	distribution of infecteds according to the number of partners per year and the time since infection,
$A(t,\tau)$	:	distribution of AIDS cases according to time since AIDS began,
$i(\tau)$	:	probability of infection from a contact with a person infected τ years ago,
$\gamma(\tau)$	:	rate at which infecteds develop AIDS at a time τ after infection,
$\delta(\tau)$	:	death rate at time τ after AIDS starts,
$A_T(t)$	:	accumulated number of AIDS cases,
$N(t)$	:	number of susceptible and infected individuals without AIDS,
μ	:	death rate of individuals without AIDS,
$c(r,r')$	:	total number of contacts in a partnership between people with r and r' partners per year, and
$S_o(r)$	:	density of people with r new partners per year before the AIDS virus was introduced.

Note that $S(t,r)$ and $S_o(r)$ have the units people-time/partners and $I(t,\tau,r)$ has the units people/partners. The resulting model is

$$\frac{\partial S(t,r)}{\partial t} = \mu(S_0(r) - S(t,r)) - \lambda(t,r)S(t,r) ,$$

$$I(t,0,r) = \lambda(t,r)S(t,r) ,$$

$$\frac{\partial I(t,\tau,r)}{\partial t} + \frac{\partial I(t,\tau,r)}{\partial \tau} = -(\gamma(\tau)+\mu)I(t,\tau,r) ,$$

$$A(t,0) = \int_0^\infty \int_0^\infty \gamma(\tau)\, I(t,\tau,r)\, d\tau dr , \tag{3.1}$$

$$\frac{\partial A(t,\tau)}{\partial t} + \frac{\partial A(t,\tau)}{\partial \tau} = -\delta(\tau)A(t) ,$$

$$\frac{dA_T}{dt} = \int_0^\infty \int_0^\infty \gamma(\tau)\, I(t,\tau,r)\, d\tau dr ,$$

$$< rN(t) > = \int_0^\infty rN(t,r)\, dr$$

and

$$N(t,r) = S(t,r) + \int_0^\infty I(t,\tau,r)\, d\tau .$$

This model portrays a community in which people mature or migrate into the susceptible community with risk r at a constant rate $\mu S_0(r)$. People without AIDS die (or become inactive) at a constant rate, with μ^{-1} their average life expectancy. Infection occurs through sexual contact with an infected partner.

There may be a wide variation in infectiousness as the disease progresses. A constant rate of progressing to AIDS would impose an exponentially decaying distribution of times to AIDS. However, cohort studies have found that the probability of getting AIDS increases with time since infection for at least the first 7 years (see Section IV.A).

The infectivity, $i(\tau)$, is an average over all individuals infected at time τ and is discussed in more detail in Section IV.B.

We must still define $\lambda(t,r)$. We discuss below some possible choices: random partner choice, a bias of people towards partners like themselves, and a combination of the two.

Defining $\lambda(t,r)$

We assume that the average r-r' partnership is sufficiently short and infectivity is sufficiently low that the probability that a person has already become infected in the partnership is small, i.e.,

$$max_{\tau} i(\tau)c(r,r') \ll 1 \ .$$

Furthermore, the epidemic cannot grow so fast that the chance that a partner is infected becomes significantly different during the course of the partnership from an unmatched person from the same risk group.

Under these assumptions , $\lambda(t,r)$ can be approximated by

$$\begin{aligned} \lambda(t,r) &= r \int_0^{\infty} F(t,r,r') k(t,r,r') dr' \\ k(t,r,r') &= c(r,r') \int_0^{\infty} i(\tau) \frac{I(t,\tau,r')}{N(t,r')} d\tau \ . \end{aligned} \tag{3.2}$$

Here k(t,r,r') is the probability of being infected by a partner of risk r'. F(t,r,r') is the fraction of partners of people with risk r that have risk r'. For random partner choice, this is

$$F_{random}(r,r') = r'N(t,r')[<rN(t)>]^{-1} \ . \tag{3.3}$$

If we assume that partners are chosen at random from the entire population, then $\lambda(t,r)$ is given by

$$\lambda_{random}(t,r) = \frac{r}{<rN(t)>} \int_0^{\infty} c(r,r')r' \int_0^{\infty} i(\tau) I(t,\tau,r') d\tau \, dr' \ . \tag{3.4}$$

A version of this model with no differences in partnership durations and no variability in infectiousness (c(r,r') and i(τ) constant) was first proposed by Anderson et al. (1986).

The $\lambda(t,r)$ given by Eq. (3.4) does not account for the fact that people do not choose partners at random from all groups but instead prefer partners of a certain type and choose them when available. Ideally, the partner selection in any model should be based on sociological data. This question will be discussed in more detail in a later report; as a first step towards addressing

this question we present below a model which allows a wide range of partner choices to be specified.

To account for partnership biasing, F(r,r') is determined by the fraction of partnerships from r' that are both available and acceptable. Thus, if partners of risk r' are accepted by people with risk r with a frequency f(r,r') then the fraction of partnerships available and acceptable to a person of risk r is

$$F(r,r') = f(r,r')r'N(t,r')\left[\int_0^\infty r''f(r,r'')N(t,r'')dr''\right]^{-1}. \tag{3.5}$$

There are, however, constraints on F(t,r,r'): the total rate that r-r' partnerships form, rN(t,r)F(t,r,r'), must be equal to the total rate that r'-r partnerships form. We would also like to ensure that a person from r has r partners/year. There is no unique way to do this. However, if we let the person from the lower risk group always be the one which decides on the acceptability of the partnership, then

$$F(t,r,r') = \begin{cases} \left(1 - \int_0^r F(t,r,x)dx\right) \bullet \dfrac{f(r,r')r'N(t,r')}{\int_r^\infty xf(r,x)N(t,x)d'x}, & \text{for } r < r', \\ F(t,r',r)\dfrac{r'N(t,r')}{rN(t,r)}, & \text{for } r > r' \end{cases} \tag{3.6}$$

is a reasonable choice. f(r,r') = 1 gives random mixing (3.4). Substituting Eq. (3.6) into Eq. (3.2) defines λ(t,r).

The system in Eq. (3.1) with different choices of λ(t,r) allows the implications of a wide variety of partner-selection mechanisms to be investigated.

If mixing occurred only with people from the same risk group, then the virus could not spread between groups, λ(t,r) would be equal to k(t,r,r), and the system in Eq. (3.1) would describe separate epidemics for each value of r. However, this perfect isolation is unrealistic. The mixing between people of similar, but not identical, risk behavior leads to diffusion of the virus from one group to another. Using

$$f(r,r') = \exp\left[-(1/2\varepsilon)(r-r')^2/(r+a)^2\right] \tag{3.7}$$

f(r,r') = exp [-(1/2ε) (r-r')^2/(r+a)^2] to define F and letting ε → 0 in Eq. 3.2 gives

$$\lambda(t,r) = r\left[k(t,r,r) + \frac{\varepsilon}{2(r+a)rN(t,r)}\frac{\partial}{\partial x}\left((x+a)^2 xN(t,x)\frac{\partial k(t,r,x)}{\partial x}\right)\right] \text{ at } x = r \quad (3.8)$$

to $O(\varepsilon)$.

With this λ, Eq. (3.1) becomes a partial differential equation. Although this model is only an approximation to the full system, it shows that the complex integro-differential equations of (3.1), (3.2), and (3.6) model a diffusive process. Exploring this model (and other limiting models) can help us understand much of what is occurring in the numerical simulations of the full model.

Even within the male homosexual and the IV needle-sharing communities, behavior patterns are not this simple. Depending on the community of interest, there may be a very different mixing pattern from the ones described here. An individual's behavior will change over time, and people with many partners one year may have only a few the next, or vice versa. Social groups within which mixing is strong, and between which it is weak, may cause low-activity people in one group to be infected before high-activity people in another group.

The social/nonsocial mixing behaviors modeled by Sattenspiel (1987) and Sattenspiel and Simon (1988) may also play an important role in the spread of this disease. Models with a variety of mixing assumptions need to be developed and compared, both with each other and with behavioral and serological studies, to ascertain what complexities are necessary for modeling HIV spread.

IV. MODEL PARAMETERS

The models discussed in the previous section contain a number of parameters that must be estimated in order to make calculations. Some of these parameters can be estimated fairly well (μ, γ, or $\delta(\tau)$), but for most of them only partial information is known. It is important to explore the effects of parameter changes, within plausible ranges, on the solution of these models.

A. RATE OF DEVELOPING AIDS

HIV causes a slow decline in the immune system. This picture of progressive immune-system decline indicates that most infected individuals eventually die from HIV-induced illness and that the probability that an

individual will develop AIDS depends on how long he has been infected. The time from infection to diagnosis of AIDS is extremely variable. HIV-infected adults have developed AIDS in less than 2 years and some have remained well for more than 9 years. The distribution of times between infection and clinical AIDS is only partially known because of the long times involved. In studies of patients for whom an estimate of date of infection can be made (such as hemophiliacs), the percentages developing AIDS in any given year after infection are either still increasing or are remaining roughly constant, which leads to an estimate of an average time to AIDS of at least 8 years.

We have chosen to use the Weibull distribution of Medley et al. (1987))

$$C'(\tau) = pq^p\tau^{p-1}e^{-(q\tau)^p} , \tag{4.1}$$

with p = 2.4, q = 0.11 for the times from infection to AIDS, primarily because it agrees well with the first 7 years of estimates from the portion of the San Francisco Hepatitis B cohort for whom the date of infection can be estimated (George Lemp, personal communication). This distribution, shown in Fig. 4.1, has a maximum at 7.5 years, a median value of 8 years and a mean of 8.9 years. This function is chosen such that all infected persons eventually get AIDS. If less than 100% of the infected people get AIDS, the tail of the distribution should be reduced, but the first 7 years should be left unchanged.

The rate $\gamma(\tau)$ of getting AIDS at time τ after infection is the conditional probability density given that the person has not yet developed AIDS

$$\gamma(\tau) = C'(\tau)[1-C(\tau)]^{-1} , \; C(\tau) = \int_0^\tau C'(\tau_a)d\tau_a . \tag{4.2}$$

$\gamma(\tau)$ is shown in Fig. 4.1 for the Weibull of Eq. (4.1).

B. INFECTIVITY

The infectivity may be related to the amount of free virus in the circulatory system of an infected individual. Studies indicate that the amount of free virus goes up in the first few weeks after infection (Francis et al., 1984; Sulahuddin et al., 1984) and then goes down as antibody response occurs, remaining at very low levels for years. As the immune system collapses in the year or so before AIDS develops, viral counts return to high levels (Lange et al., 1986).

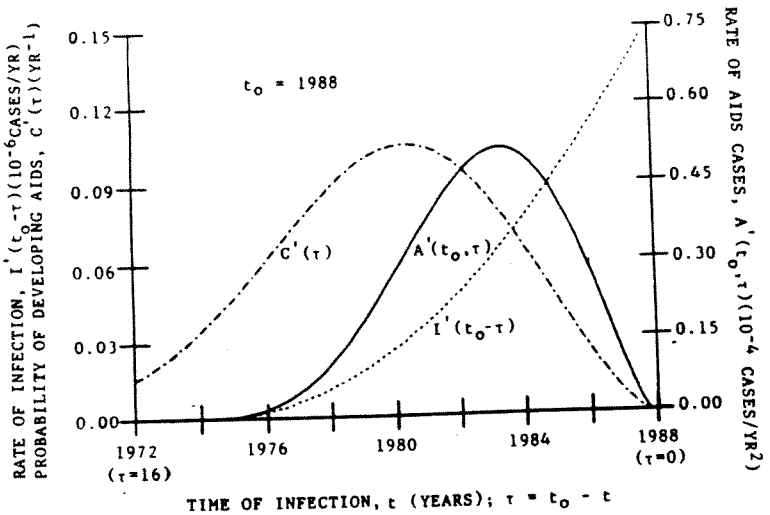

Fig. 4.1. Conversion from infection to AIDS as given by Eq. (4.1) with $p = 2.4$, $q = 0.11$. Here $C(\tau)$ is the probability of developing AIDS by τ years after infection, $C'(\tau)$ is the probability density of developing AIDS at τ years after infection, and $\gamma(\tau)$ is the conditional probability density of first developing AIDS at time τ.

Information on average per contact infectivity is only good enough to make estimates on its order of magnitude. Padian et al. (1987) have used partner studies to estimate an average per contact infectivity from man to woman of 0.001 when no other venereal diseases are present. Grant et al. (1987) have used seroprevalence estimates to estimate a per partner infectivity for man-to-man transmission (with receptive and insertive intercourse) of $i_p = 0.10$, but they had no information on numbers of contacts between partners. They also make some estimates for per contact infectivity assuming a fixed number of contacts per month and get a range of 0.004 for 8 contacts to 0.03 for 1 contact per month. Only a study with information about the number of contacts between partners and the clinical status of the partner can give actual numbers, but these data indicate that the average infectivity of a sexual contact probably lies between 0.001 and 0.03.

We assumed above that the infectiousness of a single contact, $i(\tau)$, is the average for all infected adults. The infectiousness of any single individual, $i_i(\tau)$, may have occasional ups and downs as health varies, and these variations will be smoothed out when averages are taken. More than this, there is a wide spread in the rate at which immune systems deteriorate. We define $i_i(\tau)$ as a function $i_i(\tau,\tau_a)$, which gives the immune response in terms of the individual's time to AIDS, τ_a, after infection. The time to AIDS is given by the probability distribution $C'(\tau_a)$. Comparison of a model with τ_a explicit

and our model without τ_a shows that the average infectiousness is

$$i(\tau) = \int_{\tau}^{\infty} i_i(\tau,\tau_a)C'(\tau_a)d\tau_a(1-C(\tau))^{-1}. \qquad (4.3)$$

For the (τ,r) model calculations of the next section, we have taken $i_i(\tau,\tau_a) = i^*(\tau/\tau_a)$. We use a piecewise linear infectivity, $i^*(\tau/\tau_a)$, as shown in Fig. 4.2. The solid line in Fig. 4.2 shows the effect of applying Eq. (4.3) to the Weibull of Fig. (4.1) and the $i^*(\tau/\tau_a)$ shown as $i_i(\tau,8)$.

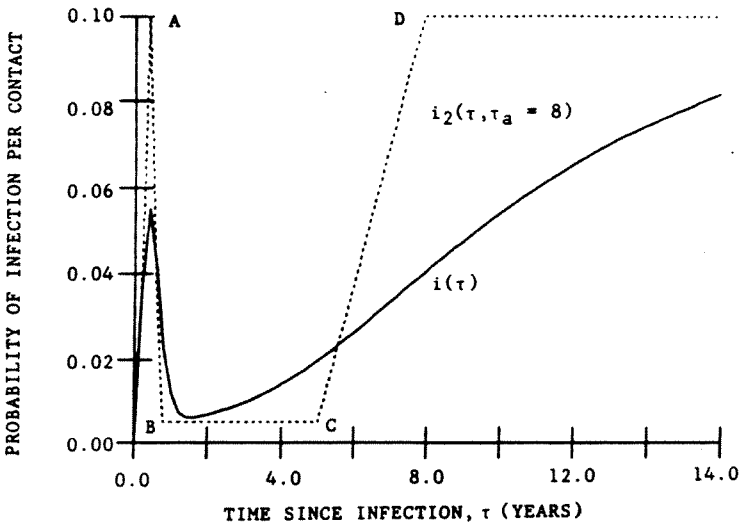

Fig. 4.2 The infectivity of an average person infected at time τ is a smeared version of the infectivity of an individual. We have postulated an individual infectivity $i_i(\tau,\tau_a) = i^*(\tau/\tau_a)$. The dotted line shows $i_i(\tau,\tau_a)$ for $\tau_a = 8$ years, and the solid line shows the average infectivity , $i(\tau)$, given by Eq. (4.3) with $C'(\tau)$ as in Fig 4.1.

C. DEATH RATES

The death rates μ and $\delta(\tau)$ are the model parameters for which the best data exist. If we take μ to represent the rate of attrition out of the at-risk community, a μ^{-1} of 30-50 years is reasonable. In our calculations, we use $\mu = 0.02$.

The probability of death once AIDS symptoms appear can be estimated from CDC mortality data, where deaths are recorded according to diagnosis date. The rate of death is high at first and gradually decreases. An exponentially decreasing probability density for death as a function of time since AIDS, which gives a constant death rate, fits adequately. A slightly

better fit is found by taking the density function to be

$$D'(\tau) = d_1 exp[-d_2 \tau (1 + d_3 \tau)^{-1}] , \tag{4.4}$$

where τ is the time since AIDS symptoms appear and $D_1 = 1$ is chosen to normalize the area to 1 at $\tau = 20$ years. Now we get the rate of death to be decreasing with τ:

$$\delta(\tau) = D'(\tau)[1 - D(\tau)]^{-1} , \quad D(\tau) = \int_0^\tau D'(\tau_d)\, d\tau_d . \tag{4.5}$$

$d_2 = 0.075$ and $d_3 = 0.05$ give reasonably good fits to the CDC data, with 48% dead in 1 year and 90% dead about 5 years later. A recent follow-up of AIDS cases found that deaths were severely under reported (Hardy et al., 1987). Thus, this distribution might underestimate the true death rate due to AIDS. This underestimate will be somewhat less severe than it might have been because of the widespread use of AZT.

D. DISTRIBUTION OF RISKS

Sexual activity data from studies of homosexual men show that there is an enormous variation between individuals in the numbers of partners and the amount and type of contacts. Participants in the Multicenter AIDS Cohort Study (MACS), who were questioned between April 1984 and March 1985, reported between 1 and 500 male partners in the previous 6 months, with a mean of between 5 and 10 (Kingsley et al., 1987). The San Francisco Men's Health Study (Winklestein et al., 1987) and homosexual men surveyed in London in 1984 and 1986 show a similar amount of variation (data from T. McManus and Carne and Weller reported in May and Anderson, 1987). A simple function that approximates most of the data is $(n+1)(n\mu)^{n+1}(n\mu+r)^{-n}$ with n between 3 and 4, and μ matched to the data. Fig. 4.3 shows this data from Carne and Weller, plus the fit with $n = 4$. For the calculations of Section V, we take $n = 4$ and a mean of 24 partners/year.

Information on the number of contacts between different types of partners (long term, casual, prostitutes) is scarce, even for these homosexual cohorts. This critical information is beginning to be collected (Joseph et al., 1987). Because transmissibility through different types of contacts may be different, the frequency of each type of contact needs to be quantified. Without such knowledge, the best that we can do is to make some reasonable assumptions and explore various possibilities.

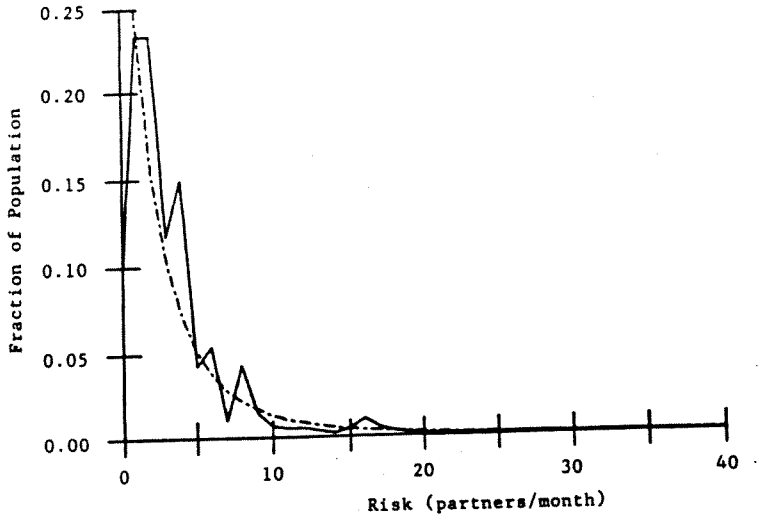

Fig.4.3. The distribution of homosexual men attending STD clinics in London, according to the number of partners per month from Carne and Weller. The dotted line shows the inverse quartic with the same mean as the data. (Data reported in May and Anderson, 1987).

The assumptions that we use are that people with large numbers of partners have one contact with each partner and that people have more contacts with each partner when both partners have fewer partners. For the calculations in this paper we use the contact function $c(r,r') = 1+(c_1-1)\exp[-c_2(r+r')]$ with $c_1 = 11$ and $c_2 = 0.1$.

E. INITIAL CONDITIONS

In order to solve system 3.1, we need to specify initial conditions for $S(0,r)$, $I(0,\tau,r)$ and $A(0,\tau,r)$. For these conditions to be consistent with the epidemic we must define infections and AIDS cases as a function of τ according to what they were at some given time.

For the calculations with no τ dependence, we take the initial infected population to be a Gaussian distribution of 1000 people, with height 100, centered at a risk behavior of 175 partners per year. For the (τ,r) model, the initial infected population should be consistent with the past history of the epidemic, as well as being consistent with the risk-model calculations. For this to hold, we define $I(0,\tau,r)$ to be such that

$$\int_0^\infty I(0,\tau,r)dr \approx (1-C(\tau))\, I'(t-\tau) \ .$$

where I'(t) is defined by Eq. (2.3): $I'(t) = a(t-t_0)^2$. The integral of $I(0,\tau,r)$ over τ is defined to have the same distribution about r = 175 partners per year as in the risk model.

V. SAMPLE CALCULATIONS

In this section we examine some of the qualitative features of the epidemic by comparing the predicted spread of HIV and AIDS cases as we vary the parameters. We focus on early growth because it is important to understand how the epidemic moves into new populations and which interactions are important in its transient dynamics. For the risk-based models, we examine the number of infecteds versus risk and show that different mixing assumptions result in substantial differences in predictions for the growth of the epidemic.

The solutions were integrated in time with an explicit Adams-Bashford-Moulton method to an accuracy of 10^{-6} per unit time. The τ-derivatives were calculated with fourth-order finite differences and the solution was approximated on a uniform grid of between 61 and 201 mesh points in both τ and r. The grid spacing and error tolerance were varied to check convergence of the solutions. We emphasize that these models are too simplistic to give accurate predictions of the AIDS epidemic and that the following calculations are meant only to illustrate the behavior of the models.

A. RISK-BASED CALCULATIONS

For our first set of calculations, we took $i(\tau)$, $\gamma(\tau)$, and $\delta(\tau)$ to be their average values ($i(\tau) = 0.025$, $\gamma(\tau) = 0.133$ years^{-1}, and $\delta(\tau) = 0.5$ years^{-1}). This allows us to reduce Eqs. 3.1 and obtain a model where the non-AIDS infecteds and the AIDS cases are distributed only according to partner change rates and not according to τ. We use this collapsed model to examine the sensitivity of the model to different choices of the acceptance functions, f(r,r').

The initial susceptible population is distributed in risk as an inverse quartic $S(0,r) = S_0\, 3(2m)^3(2m+r)^{-4}$, with total population $\int S(0,r)dr$ = 10 million, mean $m = \int rS(0,r)dr\ (10 \text{ million})^{-1} = 24$ partners/year. There is migration into all risk categories with migration rate equal to the natural

death rate, $\mu = 0.02$ times $S_0(r) = S(0,r)$. Initially, there is a Gaussian distribution of 0.001 million infected individuals, centered at risk r = 175, with height 0.0001 million - years/partner, and no AIDS cases.

First we compare acceptance functions where the width of the mixing regions are similar and increases linearly with r. These functions differ in the amount of mixing between dissimilar group. For this purpose, we use the Gaussian shown in Eq. (3.7) and

$$f(r,r') = \left[1 + \frac{(r-r')^n}{\varepsilon(r+r_m)^n}\right]^{-1} \tag{5.1}$$

with n = 2 and n = 4. Here $r_m = 10$ partners and ε is chosen so the width of the acceptance function is approximately the same for each of the three functions [$f(r,r\pm24) \approx 0.1$ at r = 75 partners/year)]. These three functions are shown in Fig. 5.1.

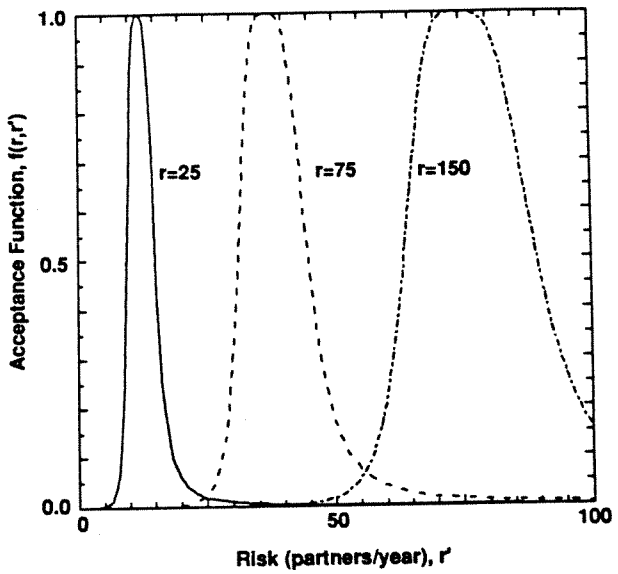

Fig. 5.1a. The inverse quartic function f(r,r') of Eq. (5.1) with n = 4, $r_m = 10$ partners/year and $\varepsilon = 0.00065$,is shown for r = 25, 75 and 150 partners/year.

These acceptance functions are based on the assumption that people preferentially mix with those similar to themselves and that more active people are less picky than the less active. Because the degree of social mixing is difficult to measure, unless the model solutions are fairly insensitive to the

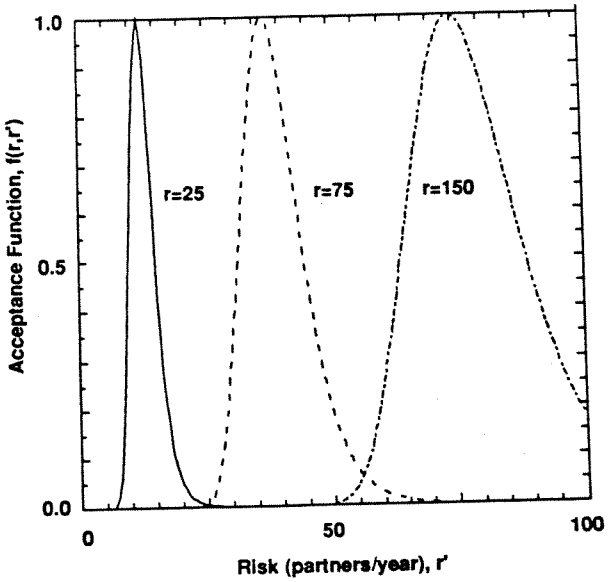

Fig. 5.1b. The Gaussian function f(r,r') of Eq. (3.7) with $\varepsilon = 0.017$ is shown, for r = 25, 75 and 150 partners/year.

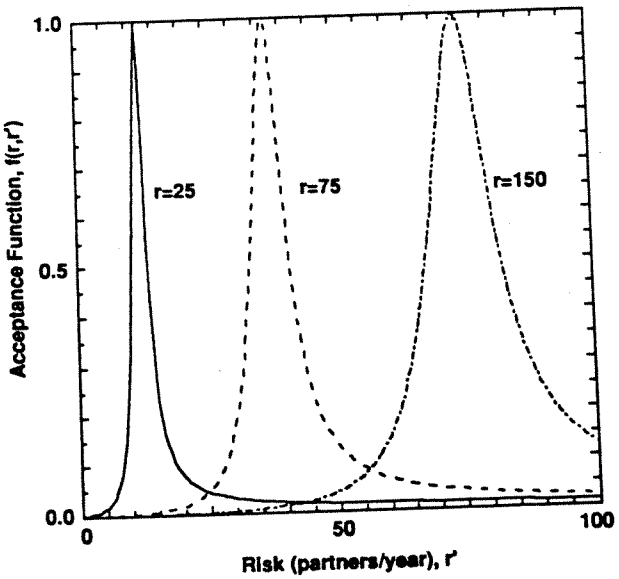

Fig. 5.1c. The inverse quadratic function f(r,r') of Eq. (5.1) with n=2, $\varepsilon = 0.0085$ is shown for r = 25, 75 and 150 partners/year.

choice of the mixing function this modeling approach can not be used reliably for quantitative predictions.

In Fig. 5.2, we show the results of the calculation for the inverse quartic acceptance function of Fig. 5.1a. Note that the epidemic grows in a nonexponential, roughly polynomial, fashion. This growth is caused by an infection wave that moves from highest risk to lower risk people, saturating each group as it moves. There are several phases to this growth: a short (1 or 2 year) fast "exponential" phase during which the highest risk groups are saturated; this is followed by "polynomial" growth period which lasts about 10 years as the wave moves downward to the lowest risk groups; a period after the epidemic wave has reached the lower risk groups and they are not yet saturated; finally, even the lowest risk groups reach saturation and drop to their equilibrium values.

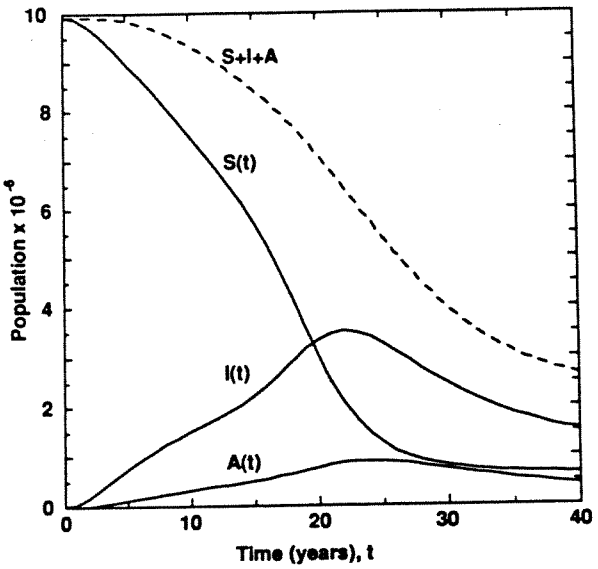

Fig. 5.2a. The change in the total populations over time for the model (3.1) when there is no dependence on time since infection and f(r,r') is defined in Fig. 5.1a.

In Fig. 5.3 we compare this calculation to those with the Gaussian and the inverse quadratic functions of Figs. 5.1b and 5.1c. We see that there is very little difference between the behavior of the exponential function and the inverse quartic. In both cases, the number infected have two inflection points before reaching a maximum and agree quantitatively. However, the quadratic function gives a faster epidemic that is more uniform in behavior and reaches low-risk groups earlier. This occurs because, although the local

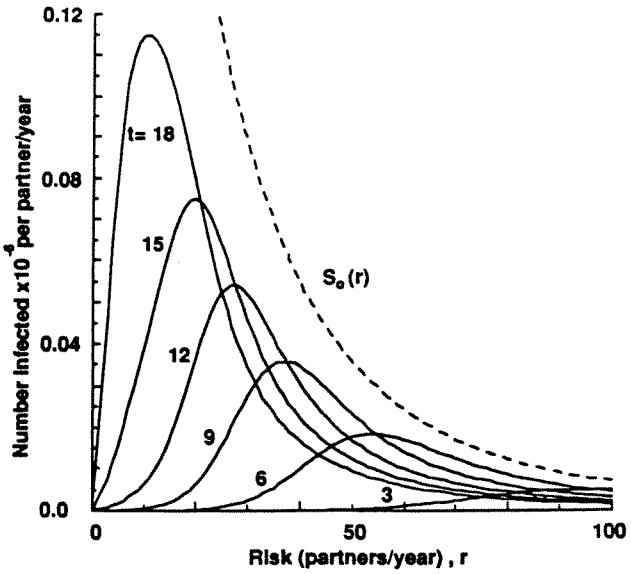

Fig. 5.2b. An infection wave moves from high risk to low risk. Shown is the infection profile at 3, 6, ..., 18 years for the calculation of Fig 5.2a.

mixing has a similar width, the long tails of the quadratic allow some mixing between high and low risk people. Thus, we see that the epidemic is fairly sensitive to even a small amount of nonself selective mixing.

To determine the sensitivity of the epidemic to the width of the mixing region, we compared the results from the inverse quartic of Figs. 5.1 and 5.2 with those for the same function when it is twice ($\varepsilon = 0.01$) and four times ($\varepsilon = 0.17$) as wide. In Fig. 5.4a we see that the initial epidemic grows faster the wider the acceptance function is. That is, the less discriminating people are in selecting partners similar to themselves, the faster the epidemic grows and spreads into the lower risk populations. The wave of infection for the wider acceptance function ($\varepsilon = 0.01$) is not as sharp as in Fig. 5.2. When $\varepsilon = 0.17$, Fig. 5.4b, the wave almost disappears and the infection quickly begins growing in the lower risk groups, as in the random mixing model ($f(r,r') = 1$) (Hyman and Stanley, 1988).

This epidemic, with $\varepsilon = 0.17$, is only slightly faster than for the quadratic of Fig. 5.1c, showing that the width of local mixing is not as important to know as the amount of mixing between very dissimilar groups. Because most of the susceptibles have low risk behavior (small r), the less selective partner choice is assumed to be, the more the partners of high-risk behavior people have low risk and the more the high-risk group acts as a pool of infection for the lower-risk group, causing the lower-risk populations to

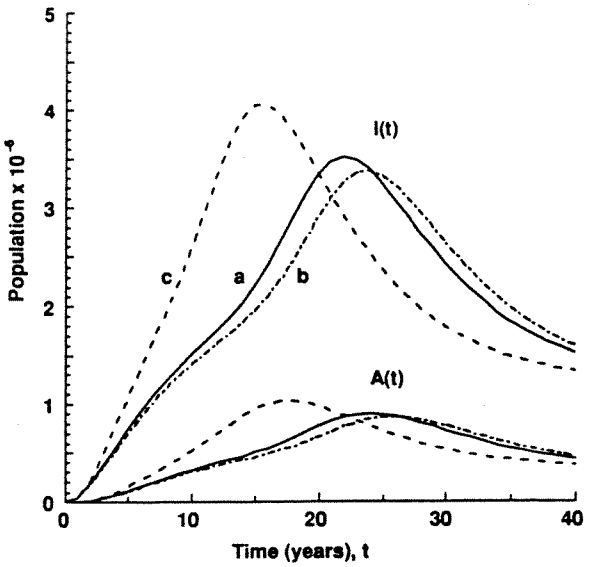

Fig. 5.3a. The total number infected and total AIDS cases for the three functions in Fig. 5.1. The letters a, b, c correspond to the acceptance functions in those of the Figures 5.1a, b, c. The small amount of mixing between low and high risk people allowed by the inverse quadratic (c) gives a faster epidemic than the inverse quartic (a) or the exponential (b), which are very similar.

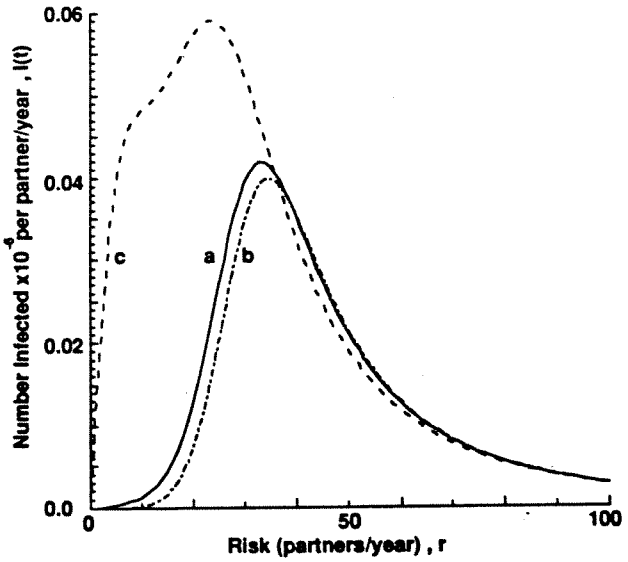

Fig. 5.3b. The distribution of infection according to risk at 10 years for the three functions of Fig. 5.1. The infection has already reached low risk groups for the inverse quartic.

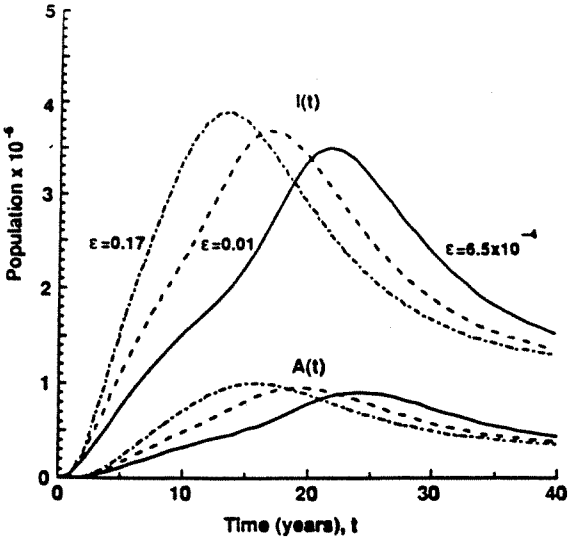

Fig. 5.4a. As the width of the acceptance function is increased, the epidemic spreads faster and saturates the population earlier. Infections and AIDS cases are shown for the calculation of Fig. 5.2 with the inverse quartic of Fig. 5.1a, an inverse quartic twice ($\varepsilon = 0.01$) and four times ($\varepsilon = 0.17$) as wide as in Fig. 5.1a.

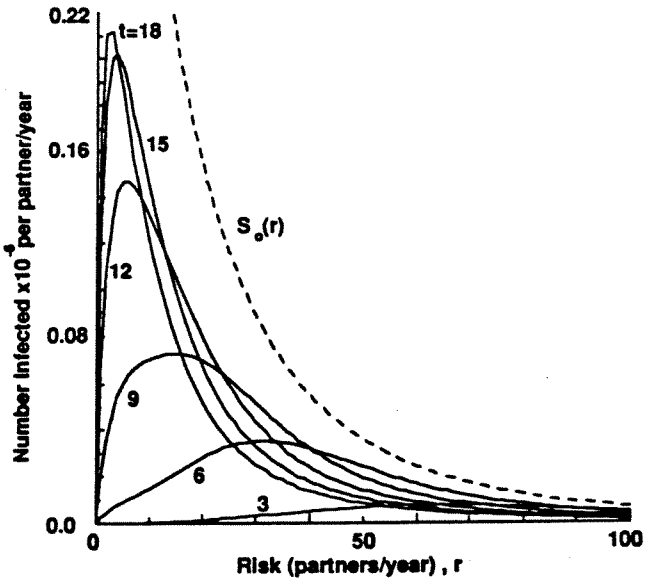

Fig. 5.4b. When the width of the acceptance function is quadrupled, the infection wave moves quickly into the lower-risk population. The distribution of infecteds versus risk is shown for $\varepsilon = 0.17$ of Fig. 5.4a at 3, 6, ..., 18 years. As the acceptance function becomes wider, the behavior approaches that of random mixing, with the wave-front behavior disappearing and there are more infected individuals with low-risk behavior than with high-risk behavior early in the epidemic.

become infected more quickly. The early AIDS cases had, on average, a large number of partners, indicating that mixing was probably fairly self-selective.

B. (τ,r) MODEL

We finish by calculating the solution of the full model in Eq. (3.1), using the same f(r,r') in λ(t,r) as for Fig. 5.2, the parameter values described in Section IV and the initial conditions

$$\begin{aligned} &\int S(0,r)dr = 10 \ , \\ &\int I(0,\tau,r)dr = \ 523.8(\tau_o - \tau)^2(1 - C(\tau)) \times 10^{-6}, \qquad \tau \le \tau_o \ , and \\ &A(0,\tau,r) = 0 \ . \end{aligned} \tag{5.2}$$

The units are millions of people and years. The scaler parameters used were $\mu = 0.02$ year^{-1} and $\tau_o = 1.8$ years. Equations (4.2) and (4.5) were used for the rates of progression from infected to AIDS and from AIDS to death. The individual infectivity $i_i(\tau,\tau_a) = i^*(\tau/\tau_a)$ in Eq. (4.3) was a piecewise linear approximation $L[(\tau_1,i_1), (\tau_2,i_2)...]$ shown as the dotted line in Fig. 4.2, which for $\tau_a = 8$ years connects the (τ,i) data points

$$i_i(\tau,\tau_a) = L[(0,0), (0.1,0), (0.4,0.1), (0.7,0.005), (5.0,0.005), (8.0,0.1)] \ . \tag{5.3}$$

This distribution and the resulting i(τ) are shown in Fig. 4.2. Note that each individual has an average per contact infectivity of 0.024. The initial conditions for $\int I(0,\tau,r)d\tau$ and $\int A(0,\tau,r)d\tau$ were the same as for the risk-based calculations. These functions were then combined using the methodology described in Sec. IV.E to define I(0,τ,r) and A(0,τ,r).

The solution in Fig. 5.5a illustrates how the susceptibles steadily decline to near-equilibrium values after 40 years. Initial growth of infecteds and AIDS cases has a somewhat different shape and the infection wave in Fig. 5.5b somewhat faster than the one in Fig. 5.2 where the average infectivity of 0.025 was used.

In Fig. 5.5d we compare the epidemic from the τ-independent calculation of Fig. 5.2 and several calculations with τ-dependence. These calculations, using the highly self-selective mixing of Fig. 5.1a, show that, at least for this special case, with a constant conversion rate and variable infectivity the epidemic is nearly identical to the τ-independent epidemic. With a constant infectivity and variable conversion rate it is significantly faster, and with both variable it is even faster. More study of the full model's sensitivites need to be undertaken.

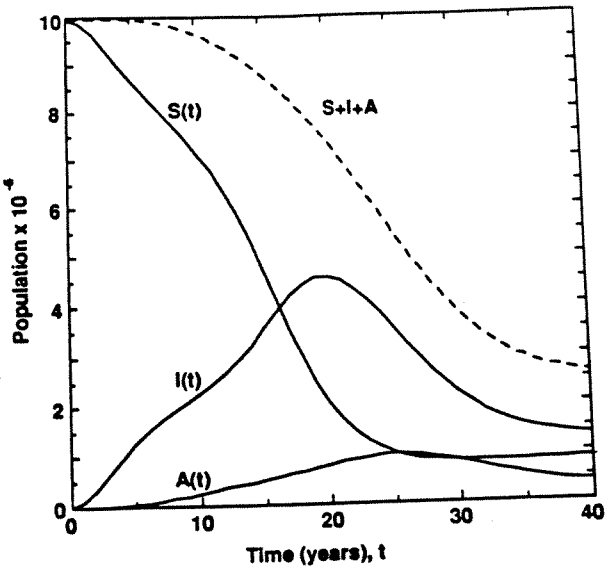

Fig. 5.5a. The solution of the model in Eqs. (3.1), (3.4) with the initial conditions $\tau_0 = 1.8$ years and infectivity as in Eq. (4.3) and $f(r,r')$ as in Fig. 5.1a. Here $S(t) = \int S(t,r)dr$, $I(t) = \int\int I(t,\tau,r)d\tau dr$ and $A(t) = \int\int A(t,\tau,r)d\tau dr$.

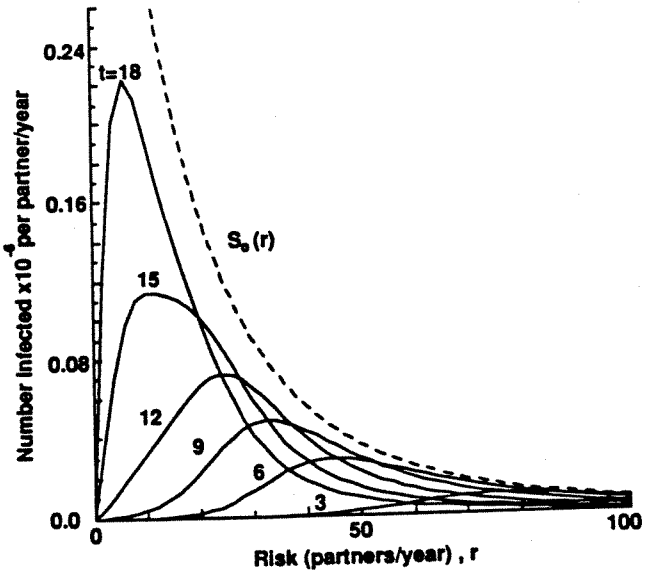

Fig. 5.5b. The infected population forms a wave that sweeps from high-risk behavior groups into lower-risk groups. The distribution of infecteds is shown every 3 years, at the times marked on the curves.

This confirms that an initial infectious period plus a 2-year delay in developing AIDS can greatly speed the epidemic. In a model where all people have the same risk behavior, we can dramatically change the rate at which the susceptible population is infected by varying the infectivity profile, even when the average infectiousness of an individual, $\int_0^1 i^*(x)dx$, is the same (Hyman and Stanley, 1988). The shape of the initial peak in infectivity is most important because more people are infected recently (low τ) than 5-7 years ago (high τ).

In Fig. 5.5c we show the distribution of the infected population as a function of time since infection. Note that there is some indication here that we may not have chosen optimal initial conditions. These distributions could be applied to make predictions of how many people will be in various stages of the disease at any given time. This is an additional benefit in including the time since infection as a variable in the model.

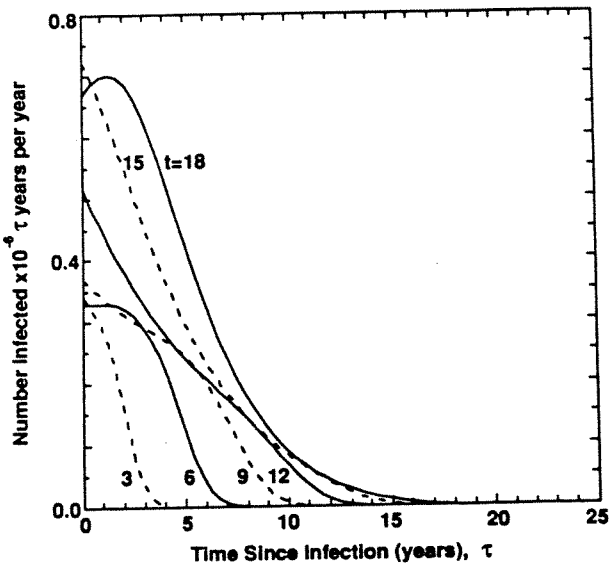

Fig. 5.5c. The distribution of infecteds $I(t,\tau) = \int I(t,\tau,r)dr$ are shown at times 3, 6, ..., 18 years, indicated on the curves.

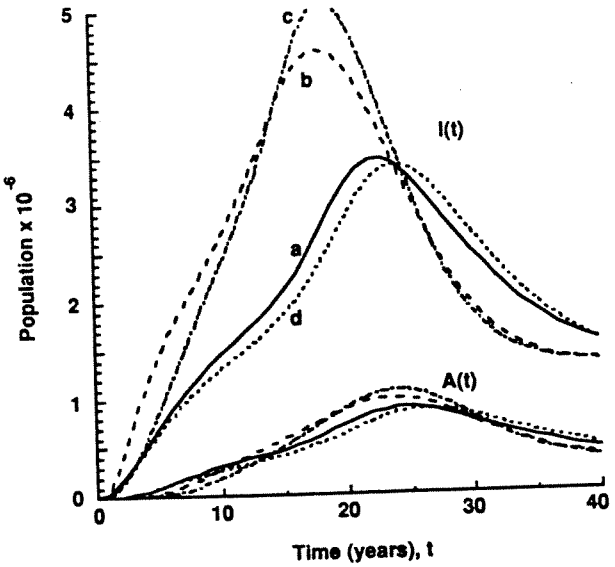

Fig. 5.5d. The infected population and AIDS cases from (a) Fig. 5.2b with no τ-dependence and i = 0.0244 (b) Fig. 5.5a with τ-dependence; (c) τ-dependence with i(τ) = 0.0244; and (d) τ-dependence with γ(τ) = 0.1333 and i(τ) as in (b). Having an initial viremic peak and no one developing AIDS for 2 years after infection greatly speeds the epidemic.

VI. SUMMARY

Major advances are required before either an effective antiviral therapy or an effective vaccine is developed and becomes widely available. Thus, we have to prepare for a long battle against the spread of the AIDS epidemic.

Mathematical models of the transmission of HIV can help researchers develop an understanding of the complex interactions that lead to the epidemic's spread. The complexity results from the long asymptomatic period after infection with the human immunodeficiency virus (HIV) that causes AIDS, the social behavior of human populations, and changes in the environment of viral transmission. These models can show how the early infection of high-risk groups, behavioral changes, and future medical advances such as treatments and vaccines will affect the future course of this epidemic. The effects will be highly nonlinear functions of the parameter values and at times may even lead to changes that are counter to both intuition and simple extrapolated predictions. The mathematical model predictions of these counterintuitive mechanisms may greatly improve our understanding of the observations.

In our computer models, the amount of sexual contact and needle-sharing between high-activity and lower-activity individuals determines both who gets infected and the speed with which the epidemic progresses. If there is little mixing between these groups, then the individuals in high-risk groups are nearly all infected before the infection moves into lower-risk groups. However, if mixing is large, many more lower-risk individuals will be infected in the early stages of the epidemic. The epidemic moves much faster when mixing is large because there are many more low-risk individuals than high-risk ones. In a model where partners are chosen with little regard for their partner-change rate, the total number of infected low-risk individuals quickly exceeds the number of infected high-risk individuals. This result is contrary to experience (Darrow et al., 1987; Goedert et al., 1984; Auerbach et al., 1984) and reflects the urgent need to collect and analyze the information on mixing patterns to estimate critical model parameters.

This sensitivity raises an obvious question: it is possible to measure mixing sufficiently accurately to predict the spread of the epidemic? We have seen that the model is not very sensitive to the shape of the mixing function, but it is very sensitive to its width. Thus, although we do not need to know whether mixing decreases in a Gaussian or a polynomial fashion as people become more dissimilar, we may need to estimate within better than a factor of two the range from which partners are primarily chosen. Even with the best possible data this may be a difficult task.

We can choose parameters in our preferential-mixing model that ensure that AIDS cases in the numerical simulations match the past history in the United States. Many other reasonable models can also quantitatively fit these cases but may predict a very different future. Quantitatively matching past AIDS cases is not, therefore, sufficient to distinguish between models. Qualitative discrepancies between AIDS cases and the model need to be explained; for example, models with initial exponential growth do not fit the U.S. AIDS case data. Correlated residuals between the fitted model predictions and AIDS data may give important clues to additional mechanisms that models must incorporate. Data from seroprevalence and cohort studies should also be consistent with the model's predictions. We plan to test the hypothesis that most mixing was between men of similar risk behavior by analyzing San Francisco data on behavior versus infection before behavior changes became widespread.

Although it is unlikely that any model will provide accurate long-term predictions of the numbers of AIDS cases, transmission models could eventually allow investigators to answer many questions. For example, one

can assume increased condom use by people in a targeted age group and region and then determine how much that increased use will slow the local course of the epidemic. This predictive ability would then help authorities decide if it is more effective to encourage condom use in that group than to use another strategy, such as stressing the importance of having fewer partners or reducing the incidence of other sexually transmitted diseases, to lower the probability of infection for some population groups. As another example, a partially effective vaccine with potentially harmful side effects might be developed. Somehow it must be ascertained which persons should be vaccinated. The model would be used to understand how vaccinating each group affects the spread of the epidemic.

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